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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,155	LAFOREST ET AL.	
	Examiner	Art Unit	
	CYNTHIA B. WILDER	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-39* is/are pending in the application.

4a) Of the above claim(s) *32-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-31 and 35-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/31/2008 and 10/11/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant preliminary amendment filed 10/11/2005 is acknowledged and has been entered. Claims 5, 9, 10, 12-14, 16, 20, 26, 28, 30-32, 34-38 have been amended. Claims 1-39 are pending.

Election/Restrictions

2. Applicant's election with traverse of Group I, claim 1-31 in the reply filed on May 23, 2008 is acknowledged. The traversal is on the ground(s) that the kit claims are linked to the method defined in claim 31. Applicant asserts tha*t* accordingly, there is no excessive burden for searching both groups of claims and withdrawal of the restriction requirement is requested. This is not found persuasive because the searches of the different inventions are not coextensive, since a search of a kit is not required for or is necessary for its use in a method of assessing copy number. Likewise, prior art which teaches the reagents of the kit as claimed would not necessarily be applicable to the method of using the kit in methods of assessing copy number. Moreover, even if the kit was known, the method of using the products may be novel and unobvious in view of the preamble and active steps.

The requirement is still deemed proper and is therefore made FINAL. Accordingly, the claims 1-31, 35-36, 38, and 39 drawn to the invention of Group I will be examined on the merit. The claims 32-34 and 37 are withdrawn from consideration as being drawn to a non-elected invention.

Claim Interpretation

The specification does not provide a specific definition of the term "sequential dispensation order of individual nucleotides", but implies throughout the specification that the term is in reference to primer extension by "pyrosequencing". Accordingly, for the purpose of application of prior art, the limitations of the "wherein clause" of the claims 1, 18, 22 and 24 is being interpreted by the examiner as performing steps of "pyrosequencing" of a target and control nucleic acid to obtain the desired information.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claims 1-9, 15-26 and 35-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Antonarakis et al (US 20030054386 A1, effective filing date June

2001). Regarding claims 1, 18, 22 and 24, Antonarakis et al teach a method comprising: a) co-amplifying a target nucleic acid sequence and a known amount of a known control nucleic acid sequence to produce respective target and control amplicons 0012-0014, 0049), wherein said control nucleic acid sequence is different than said target nucleic acid sequence (0049); and b) determining relative amounts of said respective amplicons by determining relative quantities of a primer extension reaction using each of said respective amplicons as a template, wherein said primer extension reaction is performed using steps of pyrosequencing (0014) and wherein determining relative quantities of a primer extension reaction comprises comparing a quantity of nucleotides incorporated during said primer extension reaction for said target amplicon with a quantity of nucleotides incorporated during said primer extension reaction for said control amplicon, wherein relative amounts of said respective amplicons are proportional to relative quantities of nucleotides incorporated during said primer extension reactions and said amount of said target nucleic acid sequence in said sample is proportional thereto (0078-0090). Antonarakis et al teach that the method allows detection of the relative dose of a target as compared to a known control (0049) and allows the identification of a desired target (0011). With regards to assessing copy number, Antonarakis et al recognizes the problems of prior hybridization-based methods in determining copy number. Antonarakis et al teach at paragraph 0009:

> "[I]n CGH analysis, test samples comprising labeled genomic DNA containing an unknown dose of a target genomic region and control samples comprising labeled genomic DNA containing a known dose of the target genomic region are applied to an immobilized genomic template and hybridization signals produced by the test sample and control sample are compared. The ratio of signals observed in test and control samples provides a measure of the copy number of

> the target in the genome. Although CGH offers the possibility of high throughput analysis, the method is difficult to implement since normalization between the test and control sample is critical and the sensitivity of the method is not optimal."

Antonarakis et al disclose that the method solves the problem of the prior art (see 0011). Likewise Antonarakis teaches the advantages of performing primer extension by pyrosequencing. Antonarakis et al teach "using a pyrosequencing, 96 samples can be analyzed simultaneously in less than 30 minutes". Antonarakis et al teach that "[T]he analysis does not require gel electrophoresis or any further sample processing since the output from the Pyrosequencer provides a direct quantitative ratio enabling the user to infer the genotype and hence phenotype of the individual from whom the sample is obtained. By using a paralogous gene as a natural internal control, the amount of variability from sample handling is reduced. Further, no radioactivity or labeling is required" (0086)

In view of the foregoing, one of ordinary skill in the art at the time of the claimed invention would have been motivated to utilized pyrosequencing as the quantitative PCR method to assess the amount of a known target or assess copy number of a desired target as taught by Antonarakis et al. One of ordinary skill in the art could expect to obtain predictable results in using the pyrosequencing method of Antonarakis et al based on the advantages taught by Antonarakis et al over prior known methodologies (see "Background of the Invention" at pages 1 and 2). These advantages include means of performing said method in a rapid, high-throughput manner that is amendable to semi-automated or fully automated analyses without the need for radioactivity or labeling (see 0049 and 0086).

Regarding claims 2, 19, 23 and 26, Antonarakis et al teach wherein said control nucleic acid is an endogenous nucleic acid (0086).

Regarding claims 3 and 11, Antonarakis et al teach wherein said primer extension reaction is performed using identical primers for said respective target and control amplicons (0093).

Regarding claim 4, Antonarakis et al teach wherein said primer extension can be performed using different primer pairs for each set of genes (0049).

Regarding claim 5, Antonarakis et al teach wherein said primer extension reaction is detected by detecting pyrophosphate (PPi) release (0084).

Regarding claim 6, Antonarakis et al teach wherein said pyrophosphate is detected luminometrically (0084).

Regarding claim 7, Antonarakis et al teach wherein said pyrophosphate is detected enzymatically using the enzyme luciferase as a PPi-detection enzyme (0084).

Regarding claim 8, Antonarakis et al teach wherein in the primer extension reaction, an alpha-thio analogue of an adenine nucleotide is used (0084).

Regarding claim 9, Antonarakis et al teach wherein said target nucleic acid and control nucleic acid are co-amplified using amplification primers which are immobilized or carry means for immobilization (0081).

Regarding claims 15, Antonarakis et al teach wherein each primer extension reaction yields an extension product of different lengths or sequences (0078).

Regarding claim 16, 17, 20, 21, 27, Antonarakis et al teach wherein the target nucleic acid is a gene or a fragment of a gene conferring an investigated trait (see 0014-0030 and Table 1).

Regarding claims 28-30, Antonarakis et al teach wherein the target organism is a mammalian organism, such as human (see examples at pages 10-11).

Regarding claims 31, and 35-39, Antonarakis et al teach wherein the target nucleic acid is a chromosome (see Table 1 and Abstract and Examples). Antonarakis et al do not teach wherein the target or control is an enzyme as recited in the claims 31 and 36-39. However, the claims recite a plethora of conventional nucleic acid manipulation reagents and methodologies based on the practitioner's desired results, as well as well as routine optimization of reaction components and parameters based on the practitioner's desired results. Thus, one of ordinary skill in the art would have been motivated to modify the primary references in the manner of the claims to achieve the expected benefits, optimizations an/or expanded applications based on the practitioner desired results. It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to carry out the claimed methods using any desired target or control nucleic acid based on the practitioner's desired results.

6. Claims 10-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Antonarakis et al as previously applied above and further in view of Pourmand et al (Nucleic acids Research, vol. 30, no. 7, pages e31, 2002). Regarding claim 10-14, Antonarakis et al teach the use of multiple control and target sequences that can be analyzed by the pyrosequencing methodology (see for example table 1 and 0068 and

examples. Antonarakis et al teach that 96 well can be used to perform the pyrosequencing method. Further methods of multiplex pyrosequencing in a single reaction vessel is known in the art. For example, Pourmand et al teach a multiplex pyrosequencing method. Pourmand et al teach that the method is useful because is rapid, efficient and very accurate (see discussion at pages 3, col. 2 to col. 1 of page 4). One of ordinary skill in the art at the time of the claimed invention would have been motivated to have modified the method of Antonarakis et al to encompass performing a multiplex pyrosequencing method for multiple controls and target nucleic acids based on the advantages taught by Pourmand et al that multiplex pyrosequencing is rapid, efficient and very accurate. It would be *prima facie* obvious to one of ordinary skill in the art that predictable results can be obtained in determining a target or assessing copy number.

Conclusion

7. No claims are allowed. Any inquiry concerning this communication or earlier communications from the examiner should be directed to CYNTHIA B. WILDER whose telephone number is (571)272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Cynthia B. Wilder/
Examiner Art Unit 1637